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2006-Pos Board B150

Single Molecule Studies of Oxidative Damage on Human Telomere

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Oxidative stress has been connected to aging, cancer and the development of many other diseases. Oxidative damage occurs while cellular oxidizing species concentration increases or antioxidant defenses decrease. One of the most common products of oxidative damage in DNA is 8-oxoguanine (8-oxoG). The frequent presence of 8-oxoguanine is due to the lowest oxidation potential of guanine amongst the four DNA bases. In particular, the guanine rich nature telomeric 3'-overhang sequence makes telomere more prone to the 8-oxoG damage. Therefore it provides an interesting region for studying the consequence of oxidative damage in DNA. We studied the effect of 8-oxoG lesion in human telomeric overhang which consist of repeats TTAGGG that can self-fold into G-quadruplex (GQ). The central guanine of triple-G was replaced by 8-oxoG in two repeat positions that are critical for GQ folding stability. We employed single molecule fluorescence resonance energy transfer (smFRET) to measure the changes in GQ folding stability and the resulting accessibility to telomeric proteins. Our study demonstrates that 8-oxoG replacement 1) destabilizes the structure of telomeric GQ, 2)increases the accessibility to POT1, the core component of shelterin which protects telomeric overhang and regulates telomerase activity and 3) increases the telomerase binding affinity to telomere. Overall, our results suggest that the structural instability induced by 8-oxoG lesion likely enhances telomere elongation, which may contribute to cancer development under oxidative stress.

2007-Pos Board B151

Counterion Condensation vs. Zeta Potential: Can Either Theory Describe the Electrophoresis of DNA and other Polyions?

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Many textbooks state that the electrophoretic mobility of a polyion is directly proportional to the number of charged residues and inversely proportional to its frictional coefficient. If a series of polyions differ only in the number of charged residues, the frictional coefficients will be approximately constant. Hence, the free solution mobilities are expected to be proportional to the effective charge. However, the mobilities of the charge variants of a given polyion are proportional to the logarithm of the linear charge density, not the first power of the charge. The semilogarithmic relationship between the mobility and the fractional charge of the polyion is observed for single- and double-stranded DNA oligomers, small organic molecules, protein ''ladders'' and protein sequence mutants.

Manning has used counterion condensation theory to derive an equation describing DNA electrophoretic mobility. This equation predicts that the mobilities should depend on the logarithm of the linear charge density, as observed. Surprisingly, the same equation can be used to predict the fractional mobilities of the charge variants of other types of polyions, if the square root of the surface charge density is used as the variable instead of the linear charge density. Mobilities calculated from theories of the zeta potential are less accurate than those calculated from the Manning equation. Hence, the Manning electrophoresis equation appears to have a wider validity than commonly recognized.

2008-Pos Board B152

Local Compressibility: Ground-State Predictions of Quantum Yield Trends in Azobenzene-Modified DNA

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Azobenzene incorporated into DNA has a photoisomerization quantum yield that varies as a function of the local DNA sequence and base pairing near the azobenzene attachment site. We use Molecular Dynamics computer simulations to study the effects of local free volume on photoswitching in azobenzene-modified DNA, and we find that the azobenzene quantum yield correlates strongly with the sequence-dependent variance of the local free volume. We infer that differences in quantum yield are controlled by the free energy cost of emptying the volume surrounding the azobenzene. We use our simulations to correctly predict the quantum yields for azobenzenes in several sequences not previously measured. These results will be useful in the development of a wide range of applications of photoresponsive DNA nanotechnology, ranging from controlled gene expression to DNA sensing and nanoparticle assembly.

2009-Pos Board B153

Probing the Folding Dynamics of Human Telomeric G-Quadruplex with Single-Molecule FRET

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Guanine-rich sequences consisting of several tandem repeats of TTAGGG are abundant in human telomeric DNA. They have been shown to fold into unique secondary structures under physiological conditions. One of these is the G-quadruplex structure that can undergo complex folding pathways [1-3]. Single-molecule fluorescence microscopy combined with Förster resonance energy transfer (FRET) allows for probing the conformation and dynamics of individual G-quadruplex molecules without time and population averaging and thus resolving their structural heterogeneity that is otherwise hidden in ensemble experiments [4,5].

Here we utilize single-molecule FRET microscopy to probe the K+-induced folding dynamics of human telomeric G-quadruplex DNA. Our single-molecule experiments identify several distinct FRET states populated along the folding of G-quadruplexes. We find that initial dynamic interconversion occurs between three states - the unfolded state and two transient folded states, followed by transition into a dominant long-lived folded G-quadruplex conformation. Additional single-molecule FRET measurements, employing specific chemically modified G-quadruplex sequences, and advanced molecular modeling enabled linking the experimentally observed FRET states to particular G-quadruplex conformations. Our results thus allow uncovering a possible folding pathway of the human telomeric G-quadruplex structures.

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2010-Pos Board B154

DNA-Origami Nanotubes and their Interaction with Membranes: Insights through Multiscale Molecular Dynamics Simulations

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DNA-based synthetic ion channels provide an important complement to membrane proteins for the design of biomimetic nanopores. However, base-paired self-origami channel structures have not yet been fully characterised, either experimentally or computationally. We used multiscale molecular dynamics (MD) simulation approaches to understand DNA nanotubes (DNT) and their interaction with the membranes. All-atom models have been simulated on microsecond timescales to study the conformational dynamics of a DNT in an explicit aqueous environment, revealing a consistent model of their structural and dynamic properties. At each end of the DNT gating-like motions were observed. The influence of the DNT on the diffusion of ions and water in the lumen of the pore was analysed. The DNT motions may modulate the intrinsic gating of pores when embedded in the membrane, whilst the porous nature of the DNT walls may allow lateral leakage of ions and water. These findings provide insights on the intrinsic properties of DNT structures. This in turn prompted us to initiate coarse-grained (CG) simulations to investigate the interactions of a DNT with a phospholipid bilayer. We modelled a DNT modified with a central hydrophobic belt of ~24 Å thickness, which approximately corresponds to the hydrophobic core of a phosphatidylcholine bilayer. Extended CG simulations of greater than 1 μs duration revealed that the lipophilic-DNT was stably embedded in the membrane and did not significantly perturb the lipid bilayer structure. These studies demonstrate that multiscale simulations will provide a valuable approach to investigate properties of novel DNA-based nanopores and their interactions with membrane environments.